REMARKS

Claims 18, 20-24 and 48-70 are pending in the present application, with claims 20, 51-54 and 56-59 having been withdrawn from further consideration. Accordingly, by the present communication, claim 18 has been amended. The amendment does not raise any issues of new matter, being fully supported by the Specification as filed. Accordingly, claims 18, 21-24, 48-50, 55, and 60-70 are under prosecution. Reconsideration of this Application is respectfully requested.

Based on the above amendments and the following remarks, applicant respectfully requests that the Examiner reconsider all outstanding rejections and that they be withdrawn.

Claim Amendment

Applicants have amended independent claim 18 to clarify the claim. This amendment adds no new matter. Claim 18 as amended recites, in step c): "comparing the binding pattern of the first cell lysate with the binding pattern of the second cell lysate to detect the presence of at least one protein that is differentially expressed in the first cell population with respect to the second cell population."

Support for the amendment can be found in the specification in paragraphs [0071], [0072], and [0073], which describe using arrays of uncharacterized antibodies to compare the binding patterns of different types of cell lysates. In paragraph [0073], the inventors then state:

> Antibodies reactive in one array but not the other would indicate the presence of a differentially expressed protein. This antibody is then useful for the subsequent isolation and identification of those proteins that are different in two populations of cells. [underlining added]

Applicants have amended the claim in light of the Examiner's remarks in the communication of December 29, 2004 that:

> "In response to the argument that Baecher-Allen et al. and Ekins do not teach the instant invention because they do not compare protein expression in two or more cell populations it is noted that this limitation is not recited in the instant claims. The features upon which applicant relies (i.e., protein expression) are not recited in the rejected claim(s)" (page 10 of the Office Action of December 29, 2004).

Applicants have considered that the inclusion of the comparison of protein expression as a step of the method, rather than stated as a goal of the method as set forth in the preamble of claim 18, more clearly delineates the invention. Applicants also submit that this method step (comparison of binding patterns of cell lysates of different populations to uncharacterized antibodies to detect differentially expressed proteins) sets the invention apart from the cited art, as argued below.

Claim Rejections under 35 U.S.C. §103(a)

Claims 18, 48, and 49

The Examiner has rejected claims 18, 48 and 49 as being obvious under 35 U.S.C. §103(a)over Baecher-Allan (Immunogenetics, 1993, 37/3: 182-192) in view of Ekins et al. (Clin Chem. 37/11: 1955-67, 1991). To further clarify the claims, Applicants have amended independent claim 18 to recite, as step (c) of the method: "(c) comparing the binding pattern of the first cell lysate with the binding pattern of the second cell lysate to detect the presence of at least one protein that is differentially expressed in the first cell population with respect to the second cell population".

Applicants assert that claims 18, 48, and 49 are nonobvious under the 35 U.S.C. §103(a) for at least the following reasons.

The cited references do not disclose arrays of uncharacterized antibodies, or methods in which cell lysates are applied to duplicate arrays, as recited in step (b) of amended claim 18, or

the comparison of binding patterns of two cell populations to detect the presence of a protein that is differentially expressed in the cell populations, as recited in step (c) of amended claim 18.

In Baecher-Allan et al. the binding of a particular protein to two antibodies of interest is tested by Western blotting Baecher-Allan et al. disclose testing two uncharacterized antibodies, S11 and S15, using Western blotting, to determine whether they bind a particular known protein. The authors compared the proteins or protein fragments recognized by two antibodies known to react with the particular protein of interest (mouse leukosialin/Ly-48) with the proteins or protein fragments recognized by two uncharacterized antibodies suspected of reacting with Ly-48. Because the authors' objective was to determine whether the two uncharacterized antibodies bind a particular protein, it would have been counter to their aims to apply a cell lysate to an array of uncharacterized antibodies. Such an experiment would provide no information on whether a protein of interest to the researchers (such as Ly-48), was bound by any of the uncharacterized antibodies.

In the present invention, uncharacterized antibodies are bound to duplicate arrays, to which cell lysates are hybridized. In contrast to the invention as set forth in claim 18, Baecher-Allan et al. do not disclose arrays, do not disclose an array of uncharacterized antibodies, and do not disclose applying a lysate to an array of uncharacterized antibodies.

Ekins et al. also does not dislose an array of uncharacterized antibodies. Rather, Ekins et al. provide methods for the measurement of specific analytes in a sample using characterized antibodies. Ekins et al. disclose the use of an antibody array, in which the antibodies of the array are characterized, to test a sample for the presence and amount of particular proteins or other analytes (column 2, paragraph 7: ". . . technology that will permit the simultaneous *measurement* of an unlimited number of analytes in a small biological sample such as *a single drop of blood.*" [emphasis added]). It would have been contrary to the objectives of Ekins et al. to use an array with uncharacterized antibodies, since the purpose of their technology is to measure particular

analytes. To pursue this objective, the binding properties of the antibodies on the array must be characterized.

Thus, neither Baecher-Allan et al. nor Ekins et al. disclose an array comprising uncharacterized antibodies, and no suggestion or motivation is present for substituting uncharacterized antibodies as disclosed in Baecher-Allan et al. for the characterized antibodies on an array as disclosed in Ekins et al., since the substitution would not allow one attain the objectives of either reference (characterizing an uncharacterized antibody or measuring an analyte). There is thus no suggestion or motivation in either reference to apply cell lysates to arrays of uncharacterized antibodies.

The objectives of the present invention, as set forth in amended claim 18, are distinct from those presented in the prior art. In the disclosure, the inventors provide in paragraphs [0071], [0072], and [0073]several examples of cell lysates that can be compared as to their binding pattern on arrays of uncharacterized antibodies. In paragraph [0073], the inventors then state:

> Antibodies reactive in one array but not the other would indicate the presence of a differentially expressed protein. This antibody is then useful for the subsequent isolation and identification of those proteins that are different in two populations of cells.

This indicates a different objective and novel utility for the invention, namely, the detection of proteins whose expression differs among two or more cell populations where performing a survey of differentially expressed proteins does not first require the characterization of a set of antibodies. Neither Baecher-Allan et al. nor Ekins et al. disclose, suggest, or provide motivation for the comparison of protein expression patterns of cell populations by contacting cell lysates of the two or more populations with duplicate arrays of uncharacterized antibodies.

Claims 48 and 49 recite the method of claim 18, in which the cell lysates being compared are from a single tissue type but from different species, and in which the cell lysates being compared are from a single species but from different tissue types, respectively. The Examiner has not provided a rationale for rejection of these claims. Applicants assume the rejection to be predicated on the obviousness rejection of claim 18, from which both claims depend. For the reasons set forth above, Applicants submit that claim 18, as amended is nonobvious with respect to Baecher-Allan et al. in view of Ekins et al.

Thus, each and every element of claims 18, 48 and 49 are not disclosed in the cited references. There is no suggestion to combine the references to use an array of uncharacterized antibodies for the hybridization of cell lysates, nor would one skilled in the art be motivated to do so, since the methods of Baecher-Allan et al. and Ekins et al. are significantly different from those of claim 18 and serve different objectives.

Thus, Applicants respectfully submit that the requirements of a 35 U.S.C. §103(a) rejection are not met for these claims. Applicants therefore respectfully request that the rejection of claims 18, 48, and 49 be removed.

Claims 21, 23 and 24

The Examiner has rejected claims 21, 23, and 24 as being obvious under 35 U.S.C. §103(a)over Baecher-Allan (Immunogenetics, 1993, 37/3: 182-192) in view of Ekins et al. (Clin Chem. 37/11: 1955-67, 1991), and further in view of Yates et al. (U.S. Patent No. 5,538,897). Applicants regard the rejection as applying to claims 21 and 23, as the subject matter of those claims (normal v. abnormal cells, resting state v. stimulated cells) is referred to in the rejection arguments (Section III of the Office Action). Claim 24, cited in the rejection, pertains to the use of labels, not referred to in the rejection arguments.

Applicants do not agree that Baecher-Allan et al., Ekins et al. and Yates et al., alone or in combination, render claims 21 and 23 obvious for at least the following reasons.

First, claims 21 and 23 depend directly or indirectly from claim 18 and therefore incorporate all the elements of claim 18, including step (c) "comparing the binding pattern of the first cell lysate with the binding pattern of the second cell lysate to detect the presence of at least one protein that is differentially expressed in the first cell population with respect to the second cell population". As argued above, for the rejection of claim 18, neither Baecher-Allan et al. nor Ekins et al. disclose suggest, or provide motivation for contacting an array of uncharacterized antibodies with a cell lysate. Yates et al. does not make up for the deficiencies of Baecher-Allan et al. and Ekins et al. In Yates, III et al. peptide fragmentation mass spectrometry spectra of one or more proteins are compared with peptide fragmentation mass spectrometry spectra of a database. The reference provides no disclosure of comparing binding patterns of cell lysates.

The Office Action of December 29, 2004 states that Yates, III et al. disclose the evaluation of binding patterns to identify amino acid sequences. Applicants respectfully submit that no binding patterns are disclosed in any of the cited references, including Yates, III. Rather, the patterns referred to by Yates, III et al. are fragmentation patterns produced by ionization of peptides in mass spectrometry. The patterns are not the result of a binding interaction of any sort.

Thus, neither Baecher-Allan et al., Ekins et al., or Yates, III et al. disclose step c) of claim 18, which is incorporated into claims 21 and 23: " comparing the binding pattern of the first cell lysate with the binding pattern of the second cell lysate."

In the technology disclosed in Yates, III et al., antibody-protein binding is *not* employed to measure cellular proteins. The '897 patent is concerned with mass spectrometry as a means to identify one or more sample proteins by its amino acid sequence. The patent includes description of affinity purification using an antibody (which requires that the antibody used be characterized) in order to separate one or more proteins from a mixture as a precursor to mass spectrometry, but does not disclose antibody binding patterns – or any binding patterns. Rather, mass spectra, based on the molecular mass of peptide fragments, are used to identify proteins by amino acid sequence of the peptide fragments.

Thus none of Baecher-Allan et al., Ekins et al., or Yates et al. disclose comparing binding patterns of cell lysates of abnormal and normal cells or unstimulated and stimulated cells, as required by claims 21 and 23, respectively. Thus, each and every element of claims 21 and 23 are not present in the cited references, and Applicants therefore respectfully request that the rejection of claims 21 and 23 under 35 U.S.C. §103(a) be removed.

No case has been made by the Examiner for the rejection of claim 24, drawn to the use of labels, and thus Applicants respectfully request that the rejection of claim 24 also be removed.

Claims 22, 50, 60-63, 69, and 70

Claims 22, 50, and 60-63, 69, and 70 stand rejected under 35 U.S.C. §103(a)over Baecher-Allan in view of Ekins et al., and further in view of Yates, III et al. and Cupo (J. Chromatogr. 569: 389-40, 1991). Applicants do not agree that Baecher-Allan et al., Ekins et al.,

Yates III et al., and Cupo, alone or in combination, render the claims obvious for at least the following reasons.

As already discussed, Baecher-Allan et al. and Ekins et al. do not teach each and every element of independent claim 18. Moreover, Applicants assert that a person skilled in the relevant arts would not be motivated to modify the method of Ekins et al. by using uncharacterized antibodies as disclosed in Baecher-Allan et al. on an array, as it would render the methods disclosed by either Ekins et al. or Baecher-Allan et al. useless for their intended purpose.

Claims 22, 50, 60-63, 69, and 70 depend directly or indirectly from claim 18, and thus incorporate all the elements of claim 18. Neither Yates, III et al., or Cupo make up for the deficiencies of Baecher-Allan et al. and Ekins et al. Comparison of binding patterns to detect the presence of differentially expressed proteins in different cell populations, as recited in step c) of amended claim 18, are not disclosed in any of the cited references, including Cupo. Cupo discloses the separation of nuclear matrix proteins of various cell types on two-dimensional gels. No binding pattern is disclosed in Cupo, as required by step c) of claim 18. In addition, the neither Yates, III et al. or Cupo provide a motivation for one skilled in the art to use an array in which the array comprises uncharacterized antibodies.

Thus, each and every limitation of claim 22, which incorporates the language of claim 18 and further recites the comparison of the binding pattern of lysates of cancer cells and normal cells, is not found in the cited references. The requirements of 35 U.S.C. §103(a) are not met, and Applicants respectfully request that the rejection be removed.

Applicants contend that a prima facie case of obviousness has not been made with respect to claim 50, which recites the comparison of binding patterns of cell lysates of the same tissue type at different developmental stages. Nevertheless, for the reasons elucidated above in the response to the rejection of claim 22, Applicants assert that each and every element of claim 50,

which incorporates the language of claim 18, in particular the use of an array of uncharacterized antibodies and comparison of binding patterns, is not found in the cited references. The requirements of 35 U.S.C. §103(a) are not met, and Applicants respectfully request that the rejection be removed.

Claim 69 recites the method of claim 18, "wherein the first cell lysate or the second cell lysate or both comprises a bacterial lysate, a parasite lysate or a virus lysate." for the reasons given above in the response to the rejection of claim 22, Applicants assert that each and every element of claim 50, which incorporates the language of claim 18, in particular the use of an array of uncharacterized antibodies and comparison of binding patterns, is not found in the cited references. The requirements of 35 U.S.C. §103(a) are not met, and Applicants respectfully request that the rejection be removed.

Claim 70 recites (incorporating language of claim 23, from which it depends) that a the first cell lysate contacted with an array of uncharacterized antibodies is a lysate of T-cells in a resting state, and that the second cell lysate contacted with an array of uncharacterized antibodies is a lysate of T-cells in a stimulated state. Claim 70 depends indirectly from claim 18, and thus arguments against obviousness of claim 18 also apply to claim 70. In addition, however, Applicants assert that none of the references disclose comparing a lysate of a resting state T-cell with a lysate of a stimulated state T-cell. Each and every claim element of claim 70 is not present in the cited references, and the requirements for rejection under are not met. Applicants therefore respectfully request that the rejection of claim 70 be removed.

Claims 60-62 recite different solid support materials. The Examiner asserts that the use of such materials is routine adjustment of the solid phase methods exhibited by the prior art. Applicants contend that claim 18, from which claims 60-62 directly or indirectly depend, is nonobvious for the reasons cited above. Thus the rejection of claims 60-62 under 35 U.S.C. §103(a)is obviated, and Applicants respectfully request that the rejection be removed. The Examiner has not made a case for the rejection of claim 63. Applicants assume that the rationale

is the same as for claims 60-62, and so contend that claim 63 is nonobvious on the same grounds presented for claims 60-62, and respectfully request that the rejection of claim 63 under 35 U.S.C. §103(a) be removed.

Claim 68

The Examiner has rejected claim 68 as being obvious under 35 U.S.C. §103(a)over Baecher-Allan in view of Ekins et al. (Clin Chem. 37/11: 1955-67, 1991), and further in view of Yates et al. and Cupo (J. Chromatogr. 569: 389-40, 1991). Applicants do not agree that Baecher-Allan et al., Ekins et al., Yates et al., and Cupo, alone or in combination, render the claim obvious for at least the following reasons.

First, claim 68 depends from claim 18. Each and every element of claim 18 has not been demonstrated in the prior art, in particular, the comparison of binding patterns of two cell lysates to detect differentially expressed proteins is not disclosed. Secondly, as discussed above, no motivation has been shown for using antibody arrays comprising uncharacterized antibodies in methods disclosed by Ekins et al.. Thus, for the reasons that claim 18 is nonobvious, claim 68 is also nonobvious.

In addition, Applicants disagree that using an arterial endothelial cell lystate and a venous endothelial cell lysate is "a mere design choice". Applicants also disagree that "the changes in cell type for evaluation are routine optimizations that are almost always determined and used in methods to test the properties of interest." To the contrary, Applicants contend that the vast majority of scientists investigating protein expression analysis have a particular biological system of interest under study (i.e., a disease model, a differentiation system, etc.) to which they then try to apply the most appropriate analysis methods. Applicants are uncertain what the

"properties of interest" are that the Examiner refers to, if not the protein expression patterns of particular cells.

Notwithstanding the objectives of a given researcher, Applicants believe the choice of arterial and venous endothelial cells for comparison is not arbitrary and not obvious. For example, many skilled in the arts of protein analysis or circulatory medicine would not expect that endothelial cells of blood vessels would exhibit differences in protein expression based on whether they resided in a vein or artery. Thus any attempt to reveal differential protein expression among these cell types is surprising and nonobvious. Applicants respectfully assert that the Examiner has not made the case for obviousness under 35 U.S.C. §103(a) by providing references that include each and every element of the rejected claim and demonstrating both motivation and reasonable expectation of success in comparing binding patterns of lysates of arterial and venous endothelial cells. Applicants therefore respectfully request that the rejection be removed.

Claims 55 and 64-67

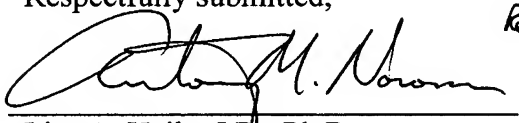
The Examiner has rejected claims 55 and 64-67 as being obvious under 35 U.S.C. §103(a)over Baecher-Allan in view of Ekins et al., and further in view of Kauvar (U.S. Patent No. 5,541,070). Applicants do not agree that Baecher-Allan et al., Ekins et al., and Kauvar, alone or in combination, render the claims obvious for at least the following reasons. Applicants contend that claim 18, from which claims 55 and 64-67 directly or indirectly depend, is nonobvious under 35 U.S.C. §103(a). Kauvar (5,541,070) does not make up for the deficiencies of Baecher-Allan and Ekins et al. as cited against claim 18, in that Kauvar, who describes selection of antibodies to an analyte of interest of particular binding specificities, does not disclose or suggest comparing the binding pattern of lysates of two or more cell populations to detect differentially expressed proteins. Therefore Applicants assert that claim 55 and 64-67,

which incorporate all the elements of claim 18, is also nonobvious under 35 U.S.C. §103(a), and respectfully request that the rejection be removed.

Conclusion

It is submitted that the proposed amendment should be entered, and that upon entry of the amendment the application is now in condition for allowance. Prompt and favorable consideration of this Amendment and Reply is therefore respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application. The Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896.

Respectfully submitted,



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